Respiratory Medicine (2008) **102**, 1355–1359

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

REVIEW

Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit

Srikumar Mallick*

University Hospital Birmingham, Harborne, Birmingham B17 0RE, UK

Received 7 March 2008; accepted 3 June 2008
Available online 17 July 2008

KEYWORDS
IPF;
Acute respiratory failure;
Ventilation;
Outcome

Summary
Idiopathic pulmonary fibrosis (IPF) is the commonest cause of interstitial lung disease. Till date there is no proven successful treatment. The prognosis is poor with a median survival of 3 years. Patients with IPF presented with acute respiratory failure are often referred to the intensive care unit for ventilatory support. Available data showed that outcome of these patients is very poor and mechanical ventilation is mostly futile. Patients and their families should be informed about the prognosis, outcome and overall outlook before making decision about ventilation and organ support. Available outcome data should be used to develop institutional and professional guidelines to help in making these difficult decisions.

Contents

* Tel.: +44 07725556403.
E-mail address: srikumarmallick@hotmail.com

0954-6111/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2008.06.003

Introduction

Idiopathic pulmonary fibrosis is the commonest form of interstitial lung disease (ILD). It is a progressive chronic disease of uncertain aetiology characterized by inflammation and fibrosis of lung parenchyma affecting gas exchange. Prognosis is poor with median survival of 3 years irrespective of treatment. IPF appears to be much more prevalent than previously reported. One previous study has reported an incidence of 6.8 per 100,000 in the United Kingdom, in 2000–2003.[1,2]

Clinical features and diagnosis

Clinical features of IPF consist of progressive dyspnoea, hypoxia with cyanosis, clubbing and end inspiratory crackles at the lung bases.

Reticular shadowings are seen on chest radiograph. Characteristic CT scan findings include reticular opacities, traction bronchiectasis and in advanced stages honeycombing and volume loss are prominent. Lung function test suggests restrictive defect with impaired gas exchange. Although diagnosis is confirmed by lung biopsy representing usual interstitial pneumonia, thoracoscopic or open lung biopsy is not necessary in presence of characteristic clinical and radiological findings.[5] Unfortunately there is no proven successful treatment. Corticosteroids and immunosuppressants have not shown any significant benefit.[27,28] As the disease progresses therapeutic intervention is mainly palliative. The only treatment proven effective in prolonging survival is lung transplantation. As patients with IPF are usually elderly and most centres limit lung transplantation to those $<$65 yr of age due to increased mortality risk[29] it is limited to minority of patients.

According to the joint statement[5] of the American Thoracic Society (ATS) and the European Respiratory Society (ERS), presence of all of the following major diagnostic criteria as well as at least 3 of the 4 minor criteria increases the likelihood of correct clinical diagnosis of IPF. The Major Criteria include (1) exclusion of other known causes of ILD, such as drug toxicities, environmental exposures, and connective tissue diseases, (2) abnormal pulmonary function studies that include evidence of restriction and impaired gas exchange, (3) bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans and (4) trans bronchial lung biopsy or bronchoalveolar lavage (BAL) showing no features to support an alternative diagnosis.

The Minor Criteria include (1) age $>$ 50 yr, (2) insidious onset of otherwise unexplained dyspnoea on exertion, (3) duration of illness $\geq$ 3 months and (4) bibasilar, inspiratory crackles (dry or 'Velcro' type in quality).

Acute deterioration

Clinical course of IPF is usually chronic and slowly progressive[3–5] but acute deterioration may occur secondary to infections, pulmonary embolism, pneumothorax, or heart failure.[6] It may also occur in half of these patients without an identifiable cause, when it is attributed to acute exacerbation of IPF.[7,8] Acute exacerbations are defined by an acute onset of dyspnoea (less than 1 month) with worsening hypoxia and progressive bilateral radiographic infiltrates seen in the absence of reversible causes.[7,9] New ground-glass infiltrates are seen on chest CT scans and diffuse alveolar damage superimposed on a background of usual interstitial pneumonia is evident on histopathology.

In a retrospective review[10] of a cohort of 147 patients with IPF, 2-year incidence of acute exacerbation was reported at 9.6%, and mortality at 78%. The time to development of acute exacerbation from the subjects' initial visits was between 3 and 60 months.

Several case reports[30,31] have suggested that acute exacerbation can be precipitated by surgical lung biopsy or bronchoalveolar lavage. In their retrospective study Kondoh et al.[33] identified 5 patients (2.1%) among 236 patients with ILD who developed acute exacerbation following surgical lung biopsy. The unexpected finding in that study was the increased and significantly greater parenchymal involvement on HRCT scan of the nonoperated lung in comparison to the operated lung and preoperative scans. This suggests factors other than surgery which includes hyperoxygenation during single lung ventilation, overdistension, ventilator associated lung injury, etc. may play a role in postoperative acute exacerbation. No studies have compared operative time, anaesthesia used, or the percentage of oxygen used to determine whether these variables are risk factors.[9] Mortality rate in patients who develop postoperative acute exacerbation is 50% or greater.[32]

Outcome from mechanical ventilation

Majority of patients with IPF are admitted in intensive care with acute respiratory failure. It is always difficult to make a decision of not to ventilate a patient referred for acute respiratory failure. There is conflict of opinion between physicians and intensivists criticising each other which ranges from inappropriate referral to prognostic pessimism.

Decision of not to ventilate usually depends on assessment of futility of care depending on poor short-term prognosis, patients wishes and the high probability of poor quality of life in the future. Before making such decision doctors usually try to look for evidence on previous outcomes in similar cases.

Evidence

A review of the literature was performed utilizing MEDLINE (via PubMed) and internet searches using key words – idiopathic pulmonary fibrosis, ventilation, outcome, and intensive care unit. Additionally, the European Respiratory Society, American Thoracic Society, and American College of Chest Physicians sites were searched for relevant abstracts. Study, patient numbers, age and outcomes were extracted from accepted studies (Table 1). The main outcome measure was mortality in intensive care and short-term mortality (within 3 months of hospital discharge).

Figures represent absolute numbers. Short-term mortality indicates mortality within 3 months of hospital discharge.

Table 1 Outcome studies on IPF patients ventilated in ICU

Study (period observed)	Number of IPF patients ventilated	Age	Number having histological confirmation of UIP	Hospital mortality	Overall short-term mortality
Blivet et al.,[11] France (1989–1998)	15	64 ± 10	7	11	13
Molina-Molina et al.,[12] Spain (1986–2002)	14	–	–	14	14
Saydain et al.,[13] USA (1995–2000)	19	68.3 ± 11.5	9	11	17
Nava and Rubini,[14] Italy	7	–	7	6	6
Stern et al.,[15] France (1991–1999)	23	52.9 mean	8	22	22
Al-Hameed and Sharma,[16] Canada (1988–2000)	25	69 ± 11	–	24	24
Fumeaux et al.,[17] Switzerland (1996–2001)	11	72 ± 8.2	4	11	11
Kim et al.,[10] South Korea (1990–2003)	9	63.4 ± 6.3	9	7	8
Pitsiou et al.,[18] Greece (2001–2005)	12	63 ± 12	–	12	12
Total	135		51	118	127

Results

Nine studies consisting of 135 patients with established diagnosis of IPF fulfilled the criteria for inclusion in the analysis. Patients those who were ventilated in intensive care are only included from these studies. Adding the individual mortality data from these studies the pooled data showed an aggregated mortality of 118 (87%) among 135 IPF patients ventilated in intensive care units. The short-term mortality (mortality within 3 months of hospital discharge) is 127 (94%). The mean duration of mechanical ventilation was 8.6 days. Of the very few patients who survived, respiratory failure was precipitated by surgery/anaesthesia in 2 patients, 1 had undergone lung transplant and 3 patients were lost in follow-up.

Two of these studies (Al-Hameed and Nava et al.) included patients where no reversible cause was found for acute respiratory failure. In one study (Fumeaux et al.) infection was presumed to be the precipitating cause in all the patients ($n = 11$). Of the remaining 92 patients – 30 had respiratory infection (bacterial and fungal), 5 pneumothorax, 4 congestive heart failure, and 2 pulmonary embolisms. Four patients developed respiratory failure following bronchoalveolar lavage, biopsy and anaesthesia. In 47 patients no precipitating factor for acute respiratory failure was found.

Exceptions (post operative respiratory failure)

A recent retrospective study involving 94 patients with ILD (of which 30 patients had IPF who were ventilated, Evans et al.[19] reported that 40% of patients with IPF survived to hospital discharge. The results are encouraging but a significant number of patients (43.6%) in this study were admitted following a surgical procedure where respiratory failure was likely to be precipitated by operative and anaesthetic complications rather than pulmonary fibrosis itself. As these patients were considered for elective surgery they were likely to have better performance status and reasonably stable pulmonary function than patients in the other studies. Seventy percent of the survivors were postsurgical patients. If we exclude this group of patients the mortality will reach nearly 90% in the remainder, similar to the other studies.

Operative mortality is low in IPF patients who undergo surgical lung biopsy for diagnostic evaluation.[35,36] Patients requiring mechanical ventilation,[35] elderly, presenting with atypical features and low diffusion capacity[34] are associated with an increased risk of death following lung biopsy.

Chiyo et al.[20] investigated the postoperative morbidity and mortality of patients with lung cancer and ILD. The 30-day mortality was only 2.8%. Similarly, Martinod et al.[21] observed no postoperative deaths in 27 patients with ILD undergoing lung cancer resection. This group of patients should be considered for ventilation like any other postsurgical patient as the condition is reversible and should not be denied life support because of underlying IPF.

Ventilatory setting

In most of the above studies the mode of ventilation used was not mentioned. In their recently published observational cohort study Fernández-Pérez and colleagues showed that high positive end expiratory pressure (PEEP) setting is associated with worse outcome. Patients with IPF has little or no recruitable lung and high PEEP is likely to cause overdistension of relatively intact lung leading to ventilator-induced lung injury (VILI). When invasive ventilation has to be used in IPF patients, like postoperative patients, patients with reversible cause of acute deterioration or where diagnosis has not been established, low tidal volume and low (PEEP) should be employed regardless of the mode of ventilation (volume controlled or pressure controlled).

Discussion

Kondoh et al.[7] in 1993 described 3 IPF patients with features of acute exacerbation. Subsequently diagnostic criteria as described above are used to identify similar patients with acute exacerbation. Many of the studies in this review included patients when the term acute exacerbation was not recognised and their condition was described as acute respiratory failure of unknown aetiology or progression of IPF. In retrospect when we look at these studies like that

of Saydian et al. where in 7 out of 10 patients no organisms recovered from BAL and histology of 6 out of 9 patients showed features of diffuse alveolar damage, these indicate that a significant number of these patients did have acute exacerbation of IPF.

Patients with IPF admitted to ICU with acute respiratory failure needing ventilation have very poor prognosis. Mechanical ventilation and life support do not seem to have any effect on mortality. Management plan should include early investigations including CT scan, echocardiogram, BAL, infection screen, etc. to look for reversible causes like pneumothrax, infection, heart failure, pulmonary embolism and to treat the cause. If these tests are negative the deterioration is attributed to acute exacerbation and be treated according to local protocol (Methyl prednisolone with Cyclophosphamide or other immunosupressants) till newer drugs with proven benefit arrives. If early intervention fails, these data suggest that outlook for survival is very poor. Mechanical ventilation is futile and patients and their families should be informed about the prognosis, outcome and overall outlook before making decision about ventilation and ITU care. Clinicians should be prepared to discuss the outcome of life support compared to comfort and palliative care with patients when they see them in an earlier stage in the clinic and document in the notes accordingly. During acute admission the risks of ventilation and the chance of surviving should be addressed if it was not done before. Most of the time this is not done before these patients are transferred to intensive care unit when it is more difficult to explain this to them and their relatives.

Intensivists should not deny life support to stable IPF patients who went into respiratory failure following a surgical procedure. They also need to remember that all interstitial lung disease patients are not IPF and non-IPF ILDs (like nonspecific interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, etc.) have a better prognosis.

Physicians, intensivists, and ethisists all agree that futile and in appropriate treatment should not be initiated even when it is requested.[22] Unfortunately there is considerable difference in opinion between clinicians regarding appropriateness of treatment for similar patients.[23] Several authors[24–26] have suggested that available outcome data should be used to develop institutional and professional guidelines to help in making these difficult decisions.

Summary points

- IPF is the commonest cause of interstitial lung disease with a median survival of 3 years, which is worse than many cancers.
- No treatment for IPF till date proven effective except lung transplant, which is limited to minority of patients.
- Acute deterioration may occur secondary to infections, pulmonary embolism, pneumothorax, or heart failure.
- It may also occur in half of these patients without an identifiable cause, when it is attributed to acute exacerbation of IPF.
- Management plan should include early investigations including CT scan, echocardiogram, BAL, infection screen, etc. to look for reversible causes.
- Available data showed that outcome of these patients in ICU is very poor and mechanical ventilation is mostly futile.
- Postsurgical patients with respiratory failure have better survival as the precipitating condition is likely reversible. They should not be denied life support because of underlying IPF.
- All the above data is from patients with IPF. Non-IPF ILDs have a better prognosis and should not be denied ventilation based on the above data.

Conflict of interest statement

No conflict of interest in relation to this review.

References

1. Gribbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. *Thorax* 2006;**61**:980–5.
2. Wells AU, Cory M. Hogaboam update in diffuse parenchymal lung disease. *Am J Respir Crit Care Med* 2007;**175**:655–60.
3. Turner-Warwick MB, Burrows AJ. Cryptogenic fibrosingalveolitis: clinical features and their influence on survival. *Thorax* 1980;**35**:171–80.
4. Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG. Natural history and untreated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978;**298**: 801–9.
5. American Thoracic Society. Idiopathic pulmonary fibrosis:diagnosis and treatment: international consensus statement. *Am J Respir Crit Care Med* 2000;**161**:646–64.
6. Panos RJ, Mortenson RL, Niccoli SA, King TE. Clinical deterioration in patients with idiopathic pulmonaryfibrosis: causes and assessment. *Am J Med* 1990;**4**:396–404.
7. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takag K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. *Chest* 1993; **103**:1808–12.
8. Tsukamoto K, Chida K, Hayakawa H, Sato A, Nakajima Y, Doi O, et al. Prediction of outcome after acute exacerbation of idiopathic interstitial pneumonia. *Nihon Kyobu Shikkan Gakkai Zasshi* 1997;**35**:746–54.
9. Hyzy R, Huang S, Myers J, Flaherty K, Martinez F. Acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2007;**132**: 1652–8.
10. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006;**27**:143–50.
11. Blivet S, Philit F, Sab JM, Langcvin B, Paret M, Guerin C, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the ICU for respiratory failure. *Chest* 2001;**120**:209–12.
12. Molina-Molina M, Badia JR, Marín-Arguedas A, Xaubet A, Santos MJ, Nicolás JM, et al. Outcomes and clinical characteristics of patients with pulmonary fibrosis and respiratory failure admitted to an intensive care unit. A study of 20 cases. *Med Clin (Barc)* 2003;**121**(2):63–7.
13. Saydain G, Islam A, Afessa B, Ryu JH, Scott JP, Peters SG. Outcome of patients with idiopathic pulmonary fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med* 2002; **166**:839–42.

14. Nava Stefano, Rubini Fiorenzo. Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. *Thorax* 1999;**54**:390—5.
15. Stern JB, Mal H, Groussard O, Brugiere O, Marceau A, Jebrak G, et al. Prognosis of patients with advanced idiopathic pulmonary fibrosis requiring mechanical ventilation for acute respiratory failure. *Chest* 2001;**120**:213—9.
16. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J* 2004;**11**:117—22.
17. Fumeaux T, Rothmeier C, Jolliet P. Outcome of mechanical ventilation for acute respiratory failure in patients with pulmonary fibrosis. *Intensive Care Med* 2001;**27**:1868—74.
18. Pitsiou G, Trigonis I, Tsiata E, Kontou P, Manolakoglou N, Stanopoulos I, et al. Argyropoulou (Thessaloniki, Greece) outcome of patients with pulmonary fibrosis admitted to the ICU for acute respiratory failure. *Eur Respir J* 2006;(28 Suppl.).
19. Fernández-Pérez ER, Yilmaz M, Jenad H, Daniels CE, Ryu JH, Hubmayr RD, et al. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. Chest, doi: 10.1378/chest.07-1481.
20. Chiyo M, Sekine Y, Iwata T, Tatsumi K, Yasufuku K, Iyoda A, et al. Impact of interstitial lung disease on surgical morbidity and mortality for lung cancer: analyses of short-term and long-term outcomes. *J Thorac Cardiovasc Surg* 2003;**126**:1141—6.
21. Martinod E, Azorin JF, Sadoun D, Destable MD, Le Toumelin P, Longchampt E. Surgical resection of lung cancer in patients with underlying interstitial lung disease. *Ann Thorac Surg* 2002;**74**:1004—7.
22. Withholding and withdrawing life-sustaining therapy. This Official Statement of the American Thoracic Society was adopted by the ATS Board of Directors, March 1991. *Am Rev Respir Dis* 1991;**144**(3 Pt 1):726—31.
23. Cook DJ, Guyatt GH, Jaeschke R, Reeve J, Spanier A, King D, et al. Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. Canadian Critical Care Trials Group. *JAMA* 1995;**273**:703—8.
24. Alpers A, Lo B. When is CPR futile? [Editorial]. *JAMA* 1995;**273**: 156—8.
25. Murphy DJ, Finucane TE. New do-not-resuscitate policies. A first step in cost control. *Arch Intern Med* 1993;**153**:1641—8.
26. Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Ann Intern Med* 1996;**125**:625—33.
27. Davies HR, Richeldi L, Walters EH. Immunomodulatory agents for idiopathic pulmonary fibrosis. *Cochrane Database Syst Rev* 2003;(3):CD003134. doi:10.1002/14651858.CD003134.
28. Richeldi L, Davies HR, Ferrara G, Franco F. Corticosteroids for idiopathic pulmonary fibrosis. *Cochrane Database Syst Rev* 2003;(3):CD002880. doi:10.1002/14651858.CD002880.
29. Gutierrez C, Al-Faifi S, Chaparro C, Waddell T, Hadjiliadis D, Singer L, et al. The effect of recipient's age on lung transplant outcome. *Am J Transplant* 2007;**7**(5):1271—7.
30. Hiwatari N, Shimura S, Takishima T, Shirato K. Bronchoalveolar lavage as a possible cause of acute exacerbation in idiopathic pulmonary fibrosis patients. *Tohoku J Exp Med* 1994;**174**: 379—86.
31. Tasaka S, Kanazawa M, Komune Y, Soejima K, Hirakata M, Yamaguchi K, et al. Acute exacerbation of subacute interstitial pneumonia after thoracoscopic lung biopsy. *Nihon Kokyuki Gakkai Zasshi* 1998;**36**:182—6.
32. Hoshikawa Y, Kondo T. Perioperative lung injury: acute exacerbation of idiopathic pulmonary fibrosis and acute interstitial pneumonia after pulmonary resection. *Nippon Geka Gakkai Zasshi* 2004;**105**:757—62.
33. Kondoh Y, Taniguchi H, Kitaichi M, Yokoi T, Johkoh T, Oishi T, et al. Acute exacerbation of interstitial pneumonia following surgical lung biopsy. *Respir Med* 2006;**100**:1753—9.
34. Utz JP, Ryu JH, Douglas WW, Hartman TE, Tazelaar HD, Myers JL, et al. High short-term mortality following lung biopsy for usual interstitial pneumonia. *Eur Respir J* 2001;**17**:175—9.
35. Lettieri CJ, Veerappan GR, Helman DL, Mulligan CR, Shorr AF. Outcomes and safety of surgical lung biopsy for interstitial lung disease. *Chest* 2005;**127**:1600—5.
36. Tiitto L, Heiskanen U, Bloigu R, Pääkkö P, Kinnula V, Kaarteenaho-Wiik R. Thoracoscopic lung biopsy is a safe procedure in diagnosing usual interstitial pneumonia. *Chest* 2005;**128**:2375—80.